L9: 1 of 14

TITLE: Particle separation method

US PAT NO: 5,536,644 DATE ISSUED: Jul. 16, 1996
[IMAGE AVAILABLE]

APPL-NO: 08/353,481 DATE FILED: Dec. 9, 1994

REL-US-DATA: Continuation of Ser. No. 787,847, Nov. 5, 1991, abandoned, which is a division of Ser. No. 533,622, Jun. 5, 1990, Pat. No. 5,076,950, which is a division of Ser. No. 262,771, Oct. 26, 1988, Pat. No. 4,935,147, which is a division of Ser. No. 811,202, Dec. 20, 1985, abandoned.

ABSTRACT:
A method is disclosed for separating a substance from a liquid medium. The method comprises combining the liquid medium containing the substance with magnetic particles under conditions for non-specific chemical binding of the magnetic particles. Thereafter, the medium is subjected to a magnetic field gradient to separate the particles from the medium. The preferred non-specific binding is achieved as the result of charge interactions between the particles usually by means of a polyionic reagent. The method of the invention has particular application to the separation of cells and microorganisms from aqueous suspensions and also to the determination of an analyte in a sample suspected of containing the analyte. The analyte is a member of a specific binding pair (sbp). The sample is combined in an assay medium with magnetic particles and a sbp member complementary to the analyte. Magnetic or non-magnetic particles capable of specific binding to the analyte or its complementary sbp member must be included in the assay medium. The combination is made under conditions for non-specifically aggregating the magnetic particles or coaggregating the magnetic and non-magnetic particles when non-magnetic particles are present. The assay medium is subjected to a magnetic field gradient to separate the aggregated particles from the medium. Then, the medium or the particles are examined for the presence or amount of the analyte or an sbp member, the binding of which is affected by the presence of the analyte.

L9: 2 of 14

TITLE: Assays utilizing sensitizer-induced production of detectable signals

US PAT NO: 5,516,636 DATE ISSUED: May 14, 1996
[IMAGE AVAILABLE]

APPL-NO: 07/984,296 DATE FILED: Dec. 1, 1992

REL-US-DATA: Continuation-in-part of Ser. No. 360,188, Jun. 1, 1989, abandoned, which is a continuation-in-part of Ser. No. 204,055, Jun. 8, 1988, abandoned.

ABSTRACT:
Specific binding assays are disclosed which utilize a sensitizer as a

label. Such sensitizers include any moiety which, when stimulated by "excitation" with radiation of one or more wavelengths or other chemical or physical stimulus (e.g., electron transfer, electrolysis, electroluminescence or energy transfer), will achieve an excited state which (a) upon interaction with molecular oxygen will produce singlet molecular oxygen, or (b) upon interaction with a leucodye will assume a reduced form which can then be returned to its original unexcited state by interaction with molecular oxygen resulting in the production of hydrogen peroxide. Either interaction with the excited sensitizer will, with the addition of other reagents, produce a detectable signal.

L9: 3 of 14

TITLE: Process for the manufacture of wholly microfabricated biosensors

US PAT NO: 5,466,575 DATE ISSUED: Nov. 14, 1995
[IMAGE AVAILABLE] DISCL-DATE: Nov. 5, 2008

APPL-NO: 07/943,345 DATE FILED: Sep. 10, 1992

REL-US-DATA: Division of Ser. No. 432,714, Nov. 7, 1989, Pat. No. 5,200,051, which is a continuation-in-part of Ser. No. 381,223, Jul. 13, 1989, abandoned, which is a continuation-in-part of Ser. No. 270,171, Nov. 14, 1988, abandoned.

ABSTRACT:
An efficient method for the microfabrication of electronic devices which have been adapted for the analyses of biologically significant analyte species is described. The techniques of the present invention allow for close control over the dimensional features of the various components and layers established on a suitable substrate. Such control extends to those parts of the devices which incorporate the biological components which enable these devices to function as biological sensors. The materials and methods disclosed herein thus provide an effective means for the mass production of uniform wholly microfabricated biosensors. Various embodiments of the devices themselves are described herein which are especially suited for real time analyses of biological samples in a clinical setting. In particular, the present invention describes assays which can be performed using certain ligand/ligand receptor-based biosensor embodiments. The present invention also discloses a novel method for the electrochemical detection of particular analyte species of biological and physiological significance using an substrate/label signal generating pair which produces a change in the concentration of electroactive species selected from the group consisting of dioxygen and hydrogen peroxide.

L9: 4 of 14

TITLE: Reversible agglutination mediators

US PAT NO: 5,405,743 DATE ISSUED: Apr. 11, 1995

[IMAGE AVAILABLE] DISCL-DATE: Mar. 14, 2006
APPL-NO: 08/267,636 DATE FILED: Jun. 29, 1994
REL-US-DATA: Continuation of Ser. No. 881,987, May 12, 1992, Pat. No. 5,370,993, which is a division of Ser. No. 278,870, Dec. 1, 1988, Pat. No. 5,136,095, which is a division of Ser. No. 51,978, May 19, 1987, Pat. No. 4,812,401.

ABSTRACT:
Compounds and methods are disclosed for reversibly aggregating particles suspended in a liquid medium. The method comprises combining the liquid medium containing the particles with a polyionic polymer capable of aggregating the particles under conditions suitable for such aggregation. Thereafter, the particles are contacted with a chemical reagent capable of cleaving the polyionic polymer under conditions sufficient to reverse the aggregation. Optionally, magnetic particles are added to the liquid medium in the present method under conditions for non-specific binding and the medium including the aggregates is subjected to a magnetic field gradient to separate the aggregates from the medium. The compounds of the present invention are polyions. The aggregation of the particles is reversible upon contact with chemical agents which cleave at least some of the bonds within the polyionic polymer.

L9: 5 of 14

TITLE: Reversible agglutination mediators
US PAT NO: 5,370,993 DATE ISSUED: Dec. 6, 1994
[IMAGE AVAILABLE]
APPL-NO: 07/881,987 DATE FILED: May 12, 1992
REL-US-DATA: Division of Ser. No. 278,870, Dec. 1, 1988, Pat. No. 5,136,095, Aug. 4, 1992, which is a division of Ser. No. 51,978, May 19, 1987, Pat. No. 4,812,401, Mar. 14, 1989.

ABSTRACT:
Compounds and methods are disclosed for reversibly aggregating particles suspended in a liquid medium. The method comprises combining the liquid medium containing the particles with a polyionic polymer capable of aggregating the particles under conditions suitable for such aggregation. Thereafter, the particles are contacted with a chemical reagent capable of cleaving the polyionic polymer under conditions sufficient to reverse the aggregation. Optionally, magnetic particles are added to the liquid medium in the present method under conditions for non-specific binding and the medium including the aggregates is subjected to a magnetic field gradient to separate the aggregates from the medium. The compounds of the present invention are polyions. The aggregation of the particles is reversible upon contact with chemical agents which cleave at least some of the bonds within the polyionic polymer.

L9: 6 of 14

TITLE: Method of forming a permselective layer
US PAT NO: 5,212,050 DATE ISSUED: May 18, 1993
[IMAGE AVAILABLE]
APPL-NO: 07/568,441 DATE FILED: Aug. 15, 1990
REL-US-DATA: Division of Ser. No. 432,714, Nov. 7, 1989, which is a continuation-in-part of Ser. No. 381,223, Jul. 13, 1989, abandoned, which is a continuation-in-part of Ser. No. 270,171, Nov. 14, 1988, abandoned.

ABSTRACT:
A method of forming a permselective layer on preselected areas of a substantially planar sensing device is disclosed. The claimed method includes establishing and confining a liquid film, derived from a silane compound mixed in a suitable solvent, within a predetermined area of the sensing device. The process relates to photolithographic imaging and developing methods coupled to a film-curing step that provides a patterned permselective layer having the desired semipermeable characteristics.

L9: 7 of 14

TITLE: Wholly microfabricated biosensors and process for the manufacture and use thereof
US PAT NO: 5,200,051 DATE ISSUED: Apr. 6, 1993
[IMAGE AVAILABLE]
APPL-NO: 07/432,714 DATE FILED: Nov. 7, 1989
REL-US-DATA: Continuation-in-part of Ser. No. 381,223, Jul. 13, 1989, abandoned, which is a continuation-in-part of Ser. No. 270,171, Nov. 14, 1988, abandoned.

ABSTRACT:
An efficient method for the microfabrication of electronic devices which have been adapted for the analyses of biologically significant analyte species is described. The techniques of the present invention allow for close control over the dimensional features of the various components and layers established on a suitable substrate. Such control extends to those parts of the devices which incorporate the biological components which enable these devices to function as biological sensors. The materials and methods disclosed herein thus provide an effective means for the mass production of uniform wholly microfabricated biosensors. Various embodiments of the devices themselves are described herein which are especially suited for real time analyses of biological samples in a clinical setting. In particular, the present invention describes assays which can be performed using certain ligand/ligand receptor-based biosensor embodiments. The present invention also discloses a novel method for the electrochemical detection of particular analyte species of biological and physiological significance using an substrate/label signal generating pair which produces a change in the concentration of

electroactive species selected from the group consisting of dioxygen and hydrogen peroxide.

L9: 8 of 14

TITLE: Reversible agglutination mediators
US PAT NO: 5,136,095 DATE ISSUED: Aug. 4, 1992
[IMAGE AVAILABLE]
APPL-NO: 07/278,870 DATE FILED: Dec. 1, 1988
REL-US-DATA: Division of Ser. No. 51,978, May 19, 1987, Pat. No. 4,812,401.

ABSTRACT:
Compounds and methods are disclosed for reversibly aggregating particles suspended in a liquid medium. The method comprises combining the liquid medium containing the particles with a polyionic polymer capable of aggregating the particles under conditions suitable for such aggregation. Thereafter, the particles are contacted with a chemical reagent capable of cleaving the polyionic polymer under conditions sufficient to reverse the aggregation. Optionally, magnetic particles are added to the liquid medium in the present method under conditions for non-specific binding and the medium including the aggregates is subjected to a magnetic field gradient to separate the aggregates from the medium. The compounds of the present invention are polyions. The aggregation of the particles is reversible upon contact with chemical agents which cleave at least some of the bonds within the polyionic polymer.

L9: 9 of 14

TITLE: Magnetic composition for particle separation
US PAT NO: 5,076,950 DATE ISSUED: Dec. 31, 1991
[IMAGE AVAILABLE]
APPL-NO: 07/533,622 DATE FILED: Jun. 5, 1990
REL-US-DATA: Division of Ser. No. 262,771, Oct. 26, 1988, Pat. No. 4,935,147, which is a continuation of Ser. No. 811,202, Dec. 20, 1985, abandoned.

ABSTRACT:
A method is disclosed for separating a substance from a liquid medium. The method comprises combining the liquid medium containing the substance with magnetic particles under conditions for non-specific chemical binding of the magnetic particles. Thereafter, the medium is subjected to a magnetic field gradient to separate the particles from the medium. The preferred non-specific binding is achieved as the result of charge interactions between the particles usually by means of a polyionic reagent. The method of the invention has particular application to the separation of cells and microorganisms from aqueous suspensions and also to the determination of an analyte in a sample suspected of containing the analyte. The analyte is a member of a specific binding pair (sbp).

The sample is combined in an assay medium with magnetic particles and a sbp member complementary to the analyte. Magnetic or non-magnetic particles capable of specific binding to the analyte or its complementary sbp member must be included in the assay medium. The combination is made under conditions for non-specifically aggregating the magnetic particles or coaggregating the magnetic and non-magnetic particles when non-magnetic particles are present. The assay medium is subjected to a magnetic field gradient to separate the aggregated particles from the medium. Then, the medium or the particles are examined for the presence or amount of the analyte or an sbp member, the binding of which is affected by the presence of the analyte.

L9: 10 of 14

TITLE: Devices for conducting specific binding assays
US PAT NO: 5,073,341 DATE ISSUED: Dec. 17, 1991
[IMAGE AVAILABLE]
APPL-NO: 07/391,796 DATE FILED: Aug. 9, 1989
REL-US-DATA: Division of Ser. No. 17,318, Feb. 20, 1987, Pat. No. 4,868,130, which is a continuation-in-part of Ser. No. 768,108, Aug. 21, 1985, abandoned.

ABSTRACT:
Methods and devices for separating bound label from unbound label within an assay mixture and for predispensing assay reactants in self-contained assay vessels, as well as a method for detecting the presence and/or amount of an analyte within a fluid sample, and a reusable detection vessel for use therein and with specific binding assays in general are disclosed. Significant to the separation of bound label from unbound label is the use of a cushion comprising generally one primary layer and in some cases one or more secondary layers.

L9: 11 of 14

TITLE: Method of manufacturing a plurality of uniform microfabricated sensing devices having an immobilized ligand receptor
US PAT NO: 5,063,081 DATE ISSUED: Nov. 5, 1991
[IMAGE AVAILABLE]
APPL-NO: 07/567,870 DATE FILED: Aug. 15, 1990
REL-US-DATA: Division of Ser. No. 432,714, Nov. 7, 1989, which is a continuation-in-part of Ser. No. 381,223, Jul. 13, 1989, abandoned, which is a continuation-in-part of Ser. No. 270,171, Nov. 14, 1988, abandoned.

ABSTRACT:
A plurality of uniform microfabricated sensing devices are produced by establishing a plurality of base sensors on a substrate wafer, forming over at least a portion of each base sensor a permselective layer,

superimposing a photoformable proteinaceous photoresist layer over a substantial portion of the permselective layer, and forming a topmost layer of an immobilized ligand receptor. The ligand receptor and corresponding ligand may be immunoreactive species.

L9: 12 of 14

TITLE: Particle separation method
US PAT NO: 4,935,147 DATE ISSUED: Jun. 19, 1990
[IMAGE AVAILABLE]
APPL-NO: 07/262,771 DATE FILED: Oct. 26, 1988
REL-US-DATA: Continuation of Ser. No. 811,202, Dec. 20, 1985, abandoned.

ABSTRACT:
A method is disclosed for separating a substance from a liquid medium. The method comprises combining the liquid medium containing the substance with magnetic particles under conditions for non-specific chemical binding of the magnetic particles. Thereafter, the medium is subjected to a magnetic field gradient to separate the particles from the medium. The preferred non-specific binding is achieved as the result of charge interactions between the particles usually by means of a polyionic reagent. The method of the invention has particular application to the separation of cells and microorganisms from aqueous suspensions and also to the determination of an analyte in a sample suspected of containing the analyte. The analyte is a member of a specific binding pair (sbp). The sample is combined in an assay medium with magnetic particles and a sbp member complementary to the analyte. Magnetic or non-magnetic particles capable of specific binding to the analyte or its complementary sbp member must be included in the assay medium. The combination is made under conditions for non-specifically aggregating the magnetic particles or coaggregating the magnetic and non-magnetic particles when non-magnetic particles are present. The assay medium is subjected to a magnetic field gradient to separate the aggregated particles from the medium. Then, the medium or the particles are examined for the presence or amount of the analyte or an sbp member, the binding of which is affected by the presence of the analyte.

L9: 13 of 14

TITLE: Methods for conducting specific binding assays
US PAT NO: 4,868,130 DATE ISSUED: Sep. 19, 1989
[IMAGE AVAILABLE]
APPL-NO: 07/017,318 DATE FILED: Feb. 20, 1987
REL-US-DATA: Continuation-in-part of Ser. No. 768,108, Aug. 21, 1985, abandoned.

ABSTRACT:
Methods and devices for separating bound label from unbound label within

an assay mixture and for predispensing assay reactants in self-contained assay vessels, as well as a method for detecting the presence and/or amount of an analyte within a fluid sample, and a reusable detection vessel for use therein and with specific binding assays in general are disclosed. Significant to the separation of bound label from unbound label is the use of a cushion comprising generally one primary layer and in some cases one or more secondary layers.

L9: 14 of 14

TITLE: Reversible agglutination mediators for separating cells from whole blood

US PAT NO: 4,812,401 DATE ISSUED: Mar. 14, 1989
[IMAGE AVAILABLE]

APPL-NO: 07/051,978 DATE FILED: May 19, 1987

ABSTRACT:
Compounds and methods are disclosed for reversibly aggregating particles suspended in a liquid medium. The method comprises combining the liquid medium containing the particles with a polyionic polymer capable of aggregating the particles under conditions suitable for such aggregation. Thereafter, the particles are contacted with a chemical reagent capable of cleaving the polyionic polymer under conditions sufficient to reverse the aggregation. Optionally, magnetic particles are added to the liquid medium in the present method under conditions for non-specific binding and the medium including the aggregates is subjected to a magnetic field gradient to separate the aggregates from the medium. The compounds of the present invention are polyions. The aggregation of the particles is reversible upon contact with chemical agents which cleave at least some of the bonds within the polyionic polymer.

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     (FILE 'USPAT' ENTERED AT 13:46:22 ON 27 AUG 96)
L1          2782 S PARAMAGNETIC
L2         48611 S ENZYME#
L3           429 S L1 AND L2
L4        201142 S FORMALIN OR ALCOHOL OR FIXATI? AGENT#
L5           163 S L3 AND L4
L6          4933 S BIOTIN
L7            72 S L5 AND L6
L8           647 S DOUBLE ANTIBODY
L9            14 S L7 AND L8
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US PAT NO: 5,536,644 [IMAGE AVAILABLE] L5: 1 of 28
TITLE: Particle **separation** method

ABSTRACT:
A method is disclosed for **separating** a substance from a liquid medium. The method comprises combining the liquid medium containing the substance with magnetic particles under conditions for non-specific chemical binding of the magnetic particles. Thereafter, the medium is subjected to a magnetic field gradient to **separate** the particles from the medium. The preferred non-specific binding is achieved as the result of charge interactions between the particles usually by means of a polyionic reagent. The method of the invention has particular application to the **separation** of cells and microorganisms from aqueous suspensions and also to the determination of an analyte in a sample suspected of containing the analyte. The analyte is a member of a specific binding pair (sbp). The sample is combined in an assay medium with magnetic particles and a sbp member complementary to the analyte. Magnetic or non-magnetic particles capable of specific binding to the analyte or its complementary sbp member must be included in the assay medium. The combination is made under conditions for non-specifically aggregating the magnetic particles or coaggregating the magnetic and non-magnetic particles when non-magnetic particles are present. The assay medium is subjected to a magnetic field gradient to **separate** the aggregated particles from the medium. Then, the medium or the particles are examined for the presence or amount of the analyte or an sbp member, the binding of which is affected by the presence of the analyte.

US PAT NO: 5,506,109 [IMAGE AVAILABLE] L5: 2 of 28
TITLE: Vitamin B12 assay

ABSTRACT:
Immunoassays for vitamin B.sub.12 using novel monoclonal antibodies to the intrinsic factor:vitamin B.sub.12 complex and to the vitamin B.sub.12 binding site on intrinsic factor.

US PAT NO: 5,422,239 [IMAGE AVAILABLE] L5: 3 of 28
TITLE: Immunoassay utilizing monoclonal high affinity IgM antibodies

ABSTRACT:
Hybridomally produced monoclonal IgM antibodies having high affinity are useful for the immunoassay and **purification** of vital antigens.

US PAT NO: 5,405,743 [IMAGE AVAILABLE] L5: 4 of 28
TITLE: Reversible agglutination mediators